

Amendments to the Specification:

Please replace the sentence beginning at page 13, line 7 and ending on page 13, line 10, with the following rewritten sentence:

-- The term "treating" in its various grammatical forms in relation to the present invention refers to preventing (*i.e.*, chemoprevention), curing, reversing, attenuating, alleviating, minimizing, suppressing or halting the deleterious effects of a disease state, disease progression, disease causative agent (*e.g.*, bacteria or viruses) or other abnormal condition. --

Please replace the section beginning at page 17, line 4 and ending on page 17, line 10, with the following rewritten section:

-- Thus, the present invention includes within its broad scope compositions comprising HDAC inhibitors which are 1) hydroxamic acid derivatives; 2) Short-Chain Fatty Acids (SCFAs); 3) cyclic tetrapeptides; 4) benzamides; 5) electrophilic ketones; and/or any other class of compounds capable of inhibiting histone deacetylases, for use in inhibiting histone deacetylase, inducing terminal differentiation, cell growth arrest and/or apoptosis in neoplastic cells, and /or inducing differentiation, cell growth arrest and/or apoptosis of tumor cells in a tumor.

Examples Non-limiting examples of such HDAC inhibitors include, but are not limited to: are set forth below. It is understood that the present invention includes any salts, crystal structures, amorphous structures, hydrates, derivatives, metabolites, stereoisomers, structural isomers, polymorphs and prodrugs of the HDAC inhibitors described herein. --

Please replace the section beginning at page 17, line 11 and ending on page 44, line 1, with the following rewritten section:

-- A. Hydroxamic Acid Derivatives such as suberoylanilide hydroxamic acid (SAHA) (Richon *et al.*, Proc. Natl. Acad. Sci. USA 95,3003-3007 (1998)); m-carboxycinnamic acid bishydroxamide (CBHA) (Richon *et al.*, *supra*); pyroxamide; trichostatin analogues such as trichostatin A (TSA) and trichostatin C (Koghe *et al.* 1998. Biochem. Pharmacol. 56: 1359-1364); salicylylhydroxamic acid

(SBHA) (Andrews *et al.*, International J. Parasitology 30,761-768 (2000)); suberoyl bishydroxamic acid (SBHA) (U.S. Patent No. 5,608,108); azelaic bishydroxamic acid (ABHA) (Andrews *et al.*, *supra*); azelaic-1-hydroxamate-9-anilide (AAHA) (Qiu *et al.*, Mol. Biol. Cell 11, 2069-2083 (2000)); 6-(3-chlorophenylureido) carpoic hydroxamic acid (3Cl-UCHA); oxamflatin [(2E)-5-[3-[(phenylsufonyl) aminol phenyl]-pent-2-en-4-ynohydroxamic acid] (Kim *et al.* Oncogene, 18: 2461 2470 (1999)); A-161906, Scriptaid (Su *et al.* 2000 Cancer Research, 60: 3137-3142); PXD-101 (Prolifix); LAQ-824; CHAP; MW2796 (Andrews *et al.*, *supra*); MW2996 (Andrews *et al.*, *supra*); or any of the hydroxamic acids disclosed in U.S. Patent Numbers 5,369,108, 5,932,616, 5,700,811, 6,087,367 and 6,511, 990.

B. Cyclic Tetrapeptides such as trapoxin A (TPX)-cyclic tetrapeptide (cyclo-(L-phenylalanyl-L-phenylalanyl-D-pipecolinyl-L-2-amino-8-oxo-9,10-epoxy decanoyl)) (Kijima *et al.*, J Biol. Chem. 268,22429-22435 (1993)); FR901228 (FK 228, depsipeptide) (Nakajima *et al.*, Ex. Cell Res. 241,126-133 (1998)); FR225497 cyclic tetrapeptide (H. Mori *et al.*, PCT Application WO 00/08048 (17 February 2000)); apicidin cyclic tetrapeptide [cyclo(N-O-methyl-L-tryptophanyl-L -isoleucinyl-D-pipecolinyl-L-2-amino-8-oxodecanoyl)] (Darkin-Rattray *et al.*, Proc. Natl. Acad. Sci. USA 93,1314313147 (1996)); apicidin Ia, apicidin Ib, apicidin Ic, apicidin IIa, and apicidin IIb (P. Dulski *et al.*, PCT Application WO 97/11366); CHAP, HC-toxin cyclic tetrapeptide (Bosch *et al.*, Plant Cell 7, 1941-1950 (1995)); WF27082 cyclic tetrapeptide (PCT Application WO 98/48825); and chlamydocin (Bosch *et al.*, *supra*).

C. Short chain fatty acid (SCFA) derivatives such as: sodium butyrate (Cousens *et al.*, J. Biol. Chem. 254,1716-1723 (1979)); isovalerate (McBain *et al.*, Biochem. Pharm. 53: 1357-1368 (1997)); valerate (McBain *et al.*, *supra*) ; 4-phenylbutyrate (4-PBA) (Lea and Tulsyan, Anticancer Research, 15,879-873 (1995)); phenylbutyrate (PB) (Wang *et al.*, Cancer Research, 59, 2766-2799 (1999)); propionate (McBain *et al.*, *supra*); butyramide (Lea and Tulsyan, *supra*); isobutyramide (Lea and Tulsyan, *supra*); phenylacetate (Lea and Tulsyan, *supra*); 3-bromopropionate (Lea and Tulsyan, *supra*); tributyrin (Guan *et al.*, Cancer Research, 60,749-755 (2000)); valproic acid-and valproate and PivanexTM.

D. Benzamide derivatives such as CI-994; MS-27-275 [N- (2-aminophenyl)-4- [N-(pyridin-3-yl methoxycarbonyl) aminomethyl] benzamide] (Saito *et al.*, Proc. Natl. Acad. Sci. USA 96, 4592-4597 (1999)); and 3'-amino derivative of MS-27-275 (Saito *et al.*, *supra*).

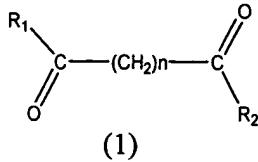
E. Electrophilic ketone derivatives such as trifluoromethyl ketones (Frey *et al.*, Bioorganic & Med. Chem. Lett. (2002), 12, 3443-3447; U.S. 6,511,990) and α -keto amides such as N-methyl- α -ketoamides

F. Other HDAC Inhibitors such as depudecinnatural products, psammoplins and depudecin (Kwon *et al.* 1998. PNAS 95: 3356-3361-3361).

Preferred hydroxamic acid based HDAC inhibitors are suberoylanilide hydroxamic acid (SAHA), m-carboxy cinnamic acid bishydroxamate (CBHA) and pyroxamide. SAHA has been shown to bind directly in the catalytic pocket of the histone deacetylase enzyme. SAHA induces cell cycle arrest, differentiation and/or apoptosis of transformed cells in culture and inhibits tumor growth in rodents. SAHA is effective at inducing these effects in both solid tumors and hematological cancers. It has been shown that SAHA is effective at inhibiting tumor growth in animals with no toxicity to the animal. The SAHA-induced inhibition of tumor growth is associated with an accumulation of acetylated histones in the tumor. SAHA is effective at inhibiting the development and continued growth of carcinogen-induced (N-methylnitrosourea) mammary tumors in rats. SAHA was administered to the rats in their diet over the 130 days of the study. Thus, SAHA is a nontoxic, orally active antitumor agent whose mechanism of action involves the inhibition of histone deacetylase activity.

Preferred HDAC inhibitors are those disclosed in U.S. Patent Numbers 5,369,108, 5,932,616, 5,700,811, 6,087,367 and 6,511, 990, issued to some of the present inventors disclose compounds, the entire contents of which are incorporated herein by reference, non-limiting examples of which are set forth below:

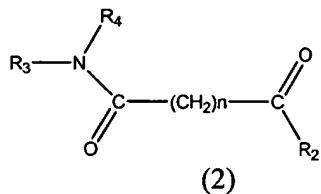
Thus, inIn one embodiment, the HDAC inhibitor useful in the methods of the present invention provides a pharmaceutical composition comprising a compoundis represented by the structure of formula 1, or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier or excipient.:



wherein R₁ and R₂ can be the same or different; when R₁ and R₂ are the same, each is a substituted or unsubstituted arylamino, cycloalkylamino, pyridineamino, piperidino, 9-purine-6-amine or thiazoleamino group; when R₁ and R₂ are different R₁=R₃-N-R₄, wherein each of R₃ and R₄ are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted, branched or unbranched alkyl, alkenyl, cycloalkyl, aryl alkyloxy, aryloxy, arylalkyloxy or pyridine group, or R₃ and R₄ are bonded together to form a piperidine group, R₂ is a hydroxylamino, hydroxyl, amino, alkylamino, dialkylamino or alkyloxy group and n is an integer from about 4 to about 8.

In a particular embodiment of Formula formula 1, R₁ and R₂ are the same and are a substituted or unsubstituted thiazoleamino group; and n is an integer from about 4 to about 8.

In another one embodiment, the HDAC inhibitor useful in the methods of the present invention provides a pharmaceutical composition comprising a compound represented by the structure of formula 2, or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier or excipient.:



wherein each of R₃ and R₄ are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted, branched or unbranched alkyl, alkenyl, cycloalkyl, arylalkyloxy, aryloxy, arylalkyloxy or pyridine group, or R₃ and R₄ are bonded together to form a piperidine group, R₂ is a hydroxylamino, hydroxyl, amino, alkylamino, dialkylamino or alkyloxy group and n is an integer from about 4 to about 8.

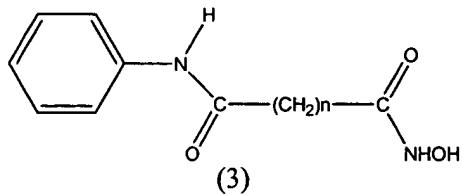
In a particular embodiment of formula 2, each of R₃ and R₄ are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted, branched or unbranched alkyl, alkenyl, cycloalkyl, aryl, alkyloxy, aryloxy, arylalkyloxy, or pyridine group, or R₃ and R₄ bond together to form a

piperidine group; R₂ is a hydroxylamino, hydroxyl, amino, alkylamino, or alkyloxy group; n is an integer from 5 to 7; and R₃-N-R₄ and R₂ are different.

In another particular embodiment of Formula formula 2, n is 6. In yet another embodiment of Formula formula II,2, R₄ is a hydrogen atom, R₃ is a substituted or unsubstituted phenyl and n is 6. In yet another embodiment of Formula formula II,2, R₄ is a hydrogen atom, R₃ is a substituted phenyl and n is 6, wherein the phenyl substituent is selected from the group consisting of a methyl, cyano, nitro, trifluoromethyl, amino, aminocarbonyl, methylcyano, chloro, fluoro, bromo, iodo, 2,3-difluoro, 2,4-difluoro, 2,5-difluoro, 3,4-difluoro, 3,5-difluoro, 2,6-difluoro, 1,2,3-trifluoro, 2,3,6-trifluoro, 2,4,6-trifluoro, 3,4,5-trifluoro, 2,3,5,6-tetrafluoro, 2,3,4,5,6-pentafluoro, azido, hexyl, t-butyl, phenyl, carboxyl, hydroxyl, methoxy, phenoxy, benzyloxy, phenylaminoxy, phenylaminocarbonyl, methoxycarbonyl, methylaminocarbonyl, dimethylamino, dimethylamino carbonyl, or hydroxylaminocarbonyl group.

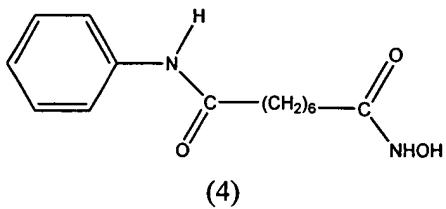
In another embodiment of formula 2, n is 6, R₄ is a hydrogen atom and R₃ is a cyclohexyl group. In another embodiment of formula 2, n is 6, R₄ is a hydrogen atom and R₃ is a methoxy group. In another embodiment of formula 2, n is 6 and R₃ and R₄ bond together to form a piperidine group. In another embodiment of formula 2, n is 6, R₄ is a hydrogen atom and R₃ is a benzyloxy group. In another embodiment of formula 2, R₄ is a hydrogen atom and R₃ is a γ -pyridine group. In another embodiment of formula 2, R₄ is a hydrogen atom and R₃ is a β -pyridine group. In another embodiment of formula 2, R₄ is a hydrogen atom and R₃ is an α -pyridine group. In another embodiment of formula 2, n is 6, and R₃ and R₄ are both methyl groups. In another embodiment of formula II,2, n is 6, R₄ is a methyl group and R₃ is a phenyl group.

In anotherone embodiment, the HDAC inhibitor useful in the methods of the present invention provides a pharmaceutical composition comprising a compoundis represented by the structure of formula 3, or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier or excipient.:

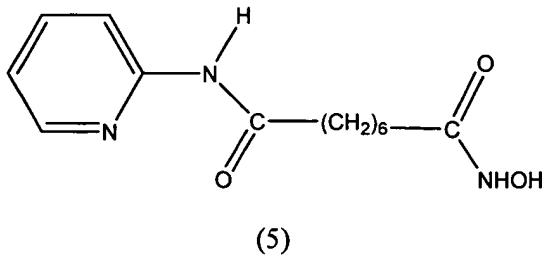


wherein n is an integer from 5 to about 8.

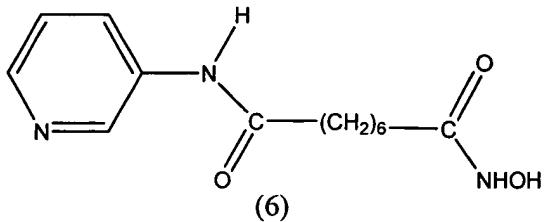
In a preferred embodiment of formula 3, n is 6. In accordance with this embodiment, the ~~present invention provides a pharmaceutical composition comprising HDAC inhibitor is SAHA (4), or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier or excipient.~~ SAHA can be represented by the following structural formula:



In ~~anotherone~~ embodiment, the ~~HDAC inhibitor useful in the methods of the present invention provides a pharmaceutical composition comprising a compound is~~ represented by the structure of formula 5, or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient.~~:

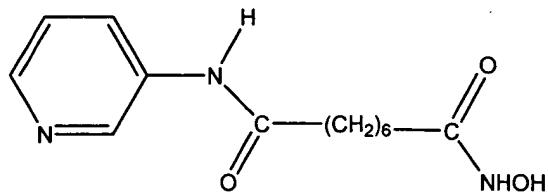


In ~~anotherone~~ embodiment, the ~~HDAC inhibitor useful in the methods of the present invention provides a pharmaceutical composition comprising a compound is~~ represented by the structure of formula 6 (pyroxamide), or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient.~~:



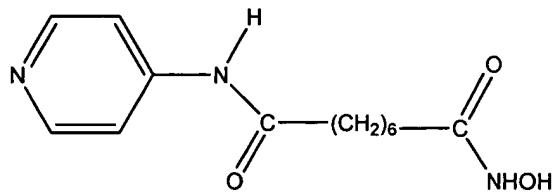
In ~~anotherone~~ embodiment, the ~~HDAC inhibitor useful in the methods of the present invention provides a pharmaceutical composition comprising a compound is~~

represented by the structure of formula 7, or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier or excipient.:



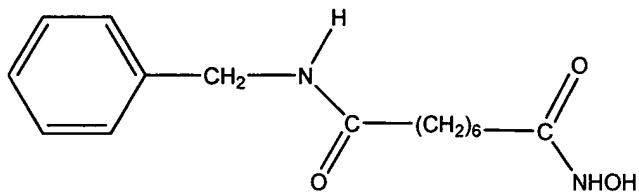
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In another one embodiment, the HDAC inhibitor useful in the methods of the present invention provides a pharmaceutical composition comprising a compound represented by the structure of formula 8, or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier or excipient.:



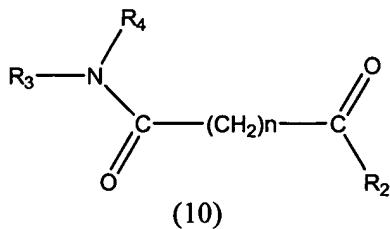
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In another one embodiment, the HDAC inhibitor useful in the methods of the present invention provides a pharmaceutical composition comprising a compound represented by the structure of formula 9, or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier or excipient.:



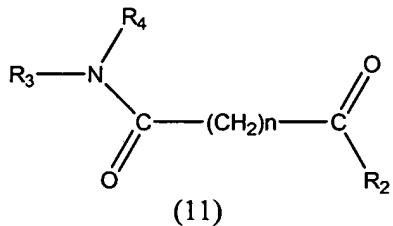
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In another one embodiment, the HDAC inhibitor useful in the methods of the present invention provides a pharmaceutical composition comprising a compound represented by the structure of formula 10, or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier or excipient.:



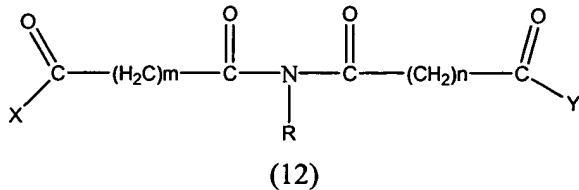
wherein R₃ is hydrogen and R₄ cycloalkyl, aryl, aryloxy, arylalkyloxy, or pyridine group, or R₃ and R₄ bond together to form a piperidine group; R₂ is a hydroxylamino group; and n is an integer from 5 to about 8.

In anotherone embodiment, the HDAC inhibitor useful in the methods of the present invention ~~provides a pharmaceutical composition comprising a compound~~ is represented by the structure of formula 11, or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient~~:



wherein R₃ and R₄ are independently a substituted or unsubstituted, branched or unbranched alkyl, alkenyl, cycloalkyl, aryl, alkyloxy, aryloxy, arylalkyloxy, or pyridine group, cycloalkyl, aryl, aryloxy, arylalkyloxy, or pyridine group, or R₃ and R₄ bond together to form a piperidine group; R₂ is a hydroxylamino group; and n is an integer from 5 to about 8.

In anotherone embodiment, the HDAC inhibitor useful in the methods of the present invention ~~provides a pharmaceutical composition comprising a compound~~ is represented by the structure of formula 12, or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient~~:

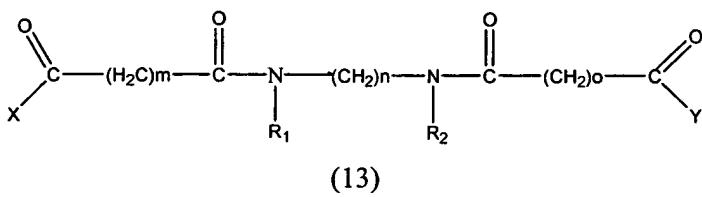


wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or

unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; R is a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, arylalkyloxy, or aryloxy group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8.

In a particular embodiment, the HDAC inhibitor is a compound of Formula formula XI12 wherein X, Y and R are each hydroxyl and both m and n are 5.

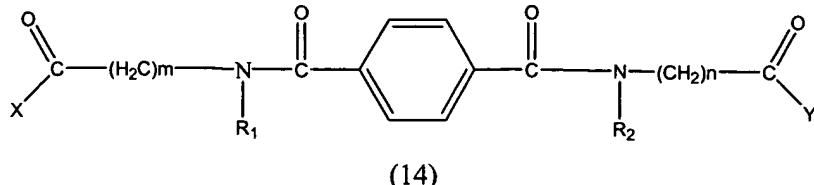
In anotherone embodiment, the HDAC inhibitor useful in the methods of the present invention provides a pharmaceutical composition comprising a compound is represented by the structure of formula 13, or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier or excipient:



wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino or aryloxyalkylamino group; each of R₁ and R₂ are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, or aryloxy group; and each of m, n and o are independently the same as or different from each other and are each an integer from about 0 to about 8.

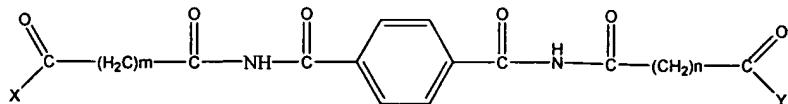
In one particular embodiment of formula 13, each of X and Y is a hydroxyl group and each of R₁ and R₂ is a methyl group. In another particular embodiment of formula 13, each of X and Y is a hydroxyl group, each of R₁ and R₂ is a methyl group, each of n and o is 6, and m is 2.

In anotherone embodiment, the HDAC inhibitor useful in the methods of the present invention provides a pharmaceutical composition comprising a compound is represented by the structure of formula 14, or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier or excipient:



wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino or aryloxyalkylamino group; each of R₁ and R₂ are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, or aryloxy group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8.

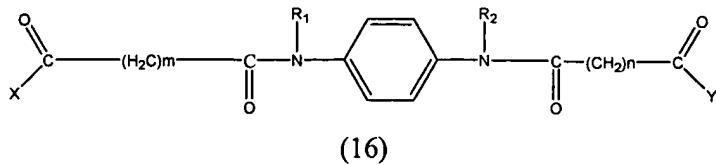
In anotherone embodiment, the HDAC inhibitor useful in the methods of the present invention provides a pharmaceutical composition comprising a compoundis represented by the structure of formula 15, or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier or excipient.:



wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino or aryloxyalkylamino group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8.

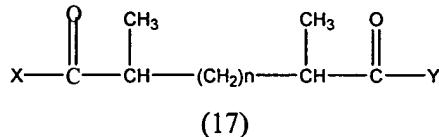
In one particular embodiment of formula 15, each of X and Y is a hydroxyl group and each of m and n is 5.

In anotherone embodiment, the HDAC inhibitor useful in the methods of the present invention provides a pharmaceutical composition comprising a compoundis represented by the structure of formula 16, or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier or excipient.:



wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino or aryloxyalkylamino group; R₁ and R₂ are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, arylalkyloxy or aryloxy group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8.

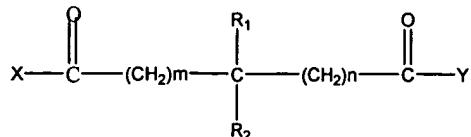
In anotherone embodiment, the HDAC inhibitor useful in the methods of the present invention provides a pharmaceutical composition comprising a compoundis represented by the structure of formula 17, or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier or excipient.:



wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, or aryloxyalkylamino group; and n is an integer from about 0 to about 8.

In one particular embodiment of formula 17, each of X and Y is a hydroxylamino group; R₁ is a methyl group, R₂ is a hydrogen atom; and each of m and n is 2. In another particular embodiment of formula 17, each of X and Y is a hydroxylamino group; R₁ is a carbonylhydroxylamino group, R₂ is a hydrogen atom; and each of m and n is 5. In another particular embodiment of formula 17, each of X and Y is a hydroxylamino group; each of R₁ and R₂ is a fluoro group; and each of m and n is 2.

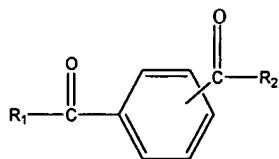
In anotherone embodiment, the HDAC inhibitor useful in the methods of the present invention provides a pharmaceutical composition comprising a compoundis represented by the structure of formula 18, or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier or excipient.:



(18)

wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkyamino or aryloxyalkylamino group; each of R₁ and R₂ are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, aryloxy, carbonylhydroxylamino or fluoro group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8.

In anotherone embodiment, the HDAC inhibitor useful in the methods of the present invention provides a pharmaceutical composition comprising a compound is represented by the structure of formula 19, or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier or excipient:

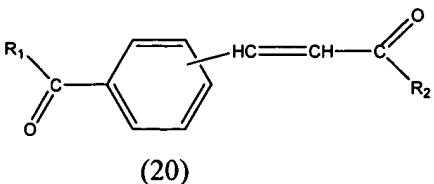


(19)

wherein each of R₁ and R₂ are independently the same as or different from each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group. In a particular embodiment, the HDAC inhibitor is a compound of structural Formula formula X19 wherein R₁ and R₂ are both hydroxylamino.

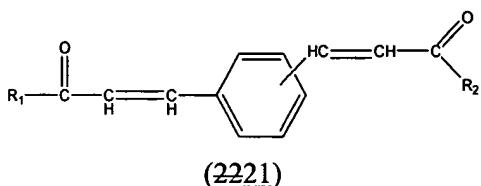
In one particular embodiment of formula 19, R₁ is a phenylamino group and R₂ is a hydroxylamino group.

In anotherone embodiment, the HDAC inhibitor useful in the methods of the present invention provides a pharmaceutical composition comprising a compound is represented by the structure of formula 20, or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier or excipient:



wherein each of R_1 and R_2 are independently the same as or different from each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group. In a particular embodiment, the HDAC inhibitor is a compound of structural Formula formula XI20 wherein R_1 and R_2 are both hydroxylamino.

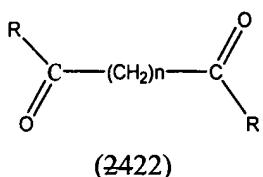
In one particular embodiment of formula XVIII, R_4 is a hydroxylamino group. In another particular embodiment of formula 21, R_2 is a hydroxylamino group. In another embodiment, the HDAC inhibitor useful in the methods of the present invention provides a pharmaceutical composition comprising a compound represented by the structure of formula 22,21, or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier or excipient.:



wherein each of R_1 and R_2 are independently the same as or different from each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group. In a particular embodiment, the HDAC inhibitor is a compound of structural Formula formula XII21 wherein R_1 and R_2 are both hydroxylamino.

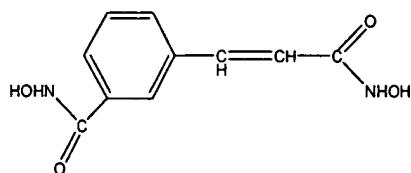
In one particular embodiment of formula 23, R_4 is a phenylamino group and R_2 is a hydroxylamino group.

In another embodiment, the HDAC inhibitor useful in the methods of the present invention provides a pharmaceutical composition comprising a compound represented by the structure of formula 24,22, or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier or excipient.:



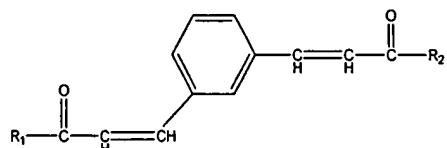
wherein R is a phenylamino group substituted with a cyano, methylcyano, nitro, carboxyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, trifluoromethyl, hydroxylaminocarbonyl, N-hydroxylaminocarbonyl, methoxycarbonyl, chloro, fluoro, methyl, methoxy, 2,3-difluoro, 2,4-difluoro, 2,5-difluoro, 2,6-difluoro, 3,5-difluoro, 2,3,6-trifluoro, 2,4,6-trifluoro, 1,2,3-trifluoro, 3,4,5-trifluoro, 2,3,4,5-tetrafluoro, or 2,3,4,5,6-pentafluoro group; and n is an integer from 4 to 8.

In another one embodiment, the HDAC inhibitor useful in the methods of the present invention provides a pharmaceutical composition comprising a compound is represented by the structure of formula 2523 (m-carboxycinnamic acid bishydroxamide - CBHA), or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier or excipient.:.



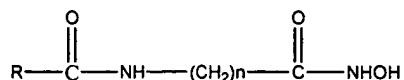
(25 23)

In another one embodiment, the HDAC inhibitor useful in the methods of the present invention provides a pharmaceutical composition comprising a compound is represented by the structure of formula 2624, or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier or excipient.:.



(24)

In another one embodiment, the HDAC inhibitor useful in the methods of the present invention provides a pharmaceutical composition comprising a compound is represented by the structure of formula 2725, or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier or excipient.:.



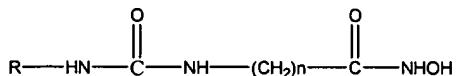
(2725)

wherein R is a substituted or unsubstituted phenyl, piperidine, thiazole, 2-pyridine, 3-pyridine or 4-pyridine and n is an integer from about 4 to about 8.

In one particular embodiment of formula 27,25, R is a substituted phenyl group. In another particular embodiment of formula 27,25, R is a substituted phenyl group, where the substituent is selected from the group consisting of methyl, cyano, nitro, thio, trifluoromethyl, amino, aminocarbonyl, methylcyano, chloro, fluoro, bromo, iodo, 2,3-difluoro, 2,4-difluoro, 2,5-difluoro, 3,4-difluoro, 3,5-difluoro, 2,6-difluoro, 1,2,3-trifluoro, 2,3,6-trifluoro, 2,4,6-trifluoro, 3,4,5-trifluoro, 2,3,5,6-tetrafluoro, 2,3,4,5,6-pentafluoro, azido, hexyl, t-butyl, phenyl, carboxyl, hydroxyl, methyloxy, phenoxy, benzyloxy, phenylaminoxy, phenylaminocarbonyl, methyloxycarbonyl, methylaminocarbonyl, dimethylamino, dimethylaminocarbonyl, or hydroxylaminocarbonyl group.

In another particular embodiment of formula 27,25, R is a substituted or unsubstituted 2-pyridine, 3-pyridine or 4-pyridine and n is an integer from about 4 to about 8.

In another embodiment, the HDAC inhibitor useful in the methods of the present invention provides a pharmaceutical composition comprising a compound represented by the structure of formula 28,26, or a pharmaceutically acceptable salt or hydrate thereof, and a pharmaceutically acceptable carrier or excipient.



(2826)

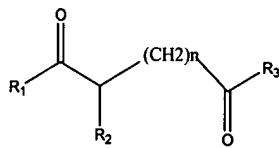
wherein R is a substituted or unsubstituted phenyl, pyridine, piperidine or thiazole group and n is an integer from about 4 to about 8 or a pharmaceutically acceptable salt thereof.

In a particular embodiment of formula 28,26, R is a substituted phenyl group. In another particular embodiment of formula 28,26, R is a substituted phenyl group, where the substituent is selected from the group consisting of methyl, cyano, nitro, thio, trifluoromethyl, amino, aminocarbonyl, methylcyano, chloro, fluoro, bromo, iodo, 2,3-difluoro, 2,4-difluoro, 2,5-difluoro, 3,4-difluoro, 3,5-difluoro, 2,6-difluoro, 1,2,3-trifluoro, 2,3,6-trifluoro, 2,4,6-trifluoro, 3,4,5-trifluoro, 2,3,5,6-tetrafluoro, 2,3,4,5,6-pentafluoro, azido, hexyl, t-butyl, phenyl, carboxyl, hydroxyl, methyloxy, phenoxy, benzyloxy, phenylaminoxy, phenylaminocarbonyl, methyloxycarbonyl, methylaminocarbonyl, dimethylamino, dimethylaminocarbonyl, or hydroxylaminocarbonyl group.

pentafluoro, azido, hexyl, t-butyl, phenyl, carboxyl, hydroxyl, methyloxy, phenoxy, benzyloxy, phenylaminoxy, phenylaminocarbonyl, methyloxycarbonyl, methylaminocarbonyl, dimethylamino, dimethylaminocarbonyl, or hydroxylaminocarbonyl group.

In another particular embodiment of formula 28,26, R is phenyl and n is 5. In another embodiment, n is 5 and R is 3-chlorophenyl.

In anotherone embodiment, the HDAC inhibitor useful in the methods of the present invention ~~provides a pharmaceutical composition comprising a compoundis~~ represented by the structure of formula 29,27, or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient.~~:

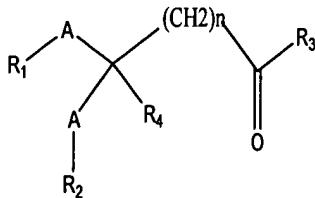


(2927)

wherein each of R₁ and R₂ is directly attached or through a linker and is substituted or unsubstituted, aryl (e.g., phenyl), arylalkyl (e.g., benzyl), naphthyl, cycloalkyl, cycloalkylamino, pyridineamino, piperidino, 9-purine-6-amino, thiazoleamino, hydroxyl, branched or unbranched alkyl, alkenyl, alkyloxy, aryloxy, arylalkyloxy, pyridyl, or quinolinyl or isoquinolinyl; n is an integer from about 3 to about 10 and R₃ is a hydroxamic acid, hydroxylamino, hydroxyl, amino, alkylamino or alkyloxy group. The linker can be an amide moiety, e.g., O-, -S-, -NH-, NR₅, -CH₂-, -(CH₂)_m-, -(CH=CH)-, phenylene, cycloalkylene, or any combination thereof, wherein R₅ is a substitute or unsubstituted C₁-C₅ alkyl.

In certain embodiments of formula 29,27, R₁ is -NH-R₄ wherein R₄ is substituted or unsubstituted, aryl (e.g., phenyl), arylalkyl (e.g., benzyl), naphthyl, cycloalkyl, cycloalkylamino, pyridineamino, piperidino, 9-purine-6-amino, thiazoleamino, hydroxyl, branched or unbranched alkyl, alkenyl, alkyloxy, aryloxy, arylalkyloxy, pyridyl, quinolinyl or isoquinolinyl.

In anotherone embodiment, the HDAC inhibitor useful in the methods of the present invention ~~provides a pharmaceutical composition comprising a compoundis~~ represented by the structure of formula 30,28, or a pharmaceutically acceptable salt or hydrate thereof, ~~and a pharmaceutically acceptable carrier or excipient.~~:

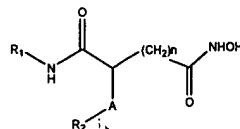


(3028)

wherein each of R₁ and R₂ is, substituted or unsubstituted, aryl (e.g., phenyl), arylalkyl (e.g., benzyl), naphthyl, cycloalkyl, cycloalkylamino, pyridineamino, piperidino, 9-purine-6-amino, thiazoleamino, hydroxyl, branched or unbranched alkyl, alkenyl, alkyloxy, aryloxy, arylalkyloxy, pyridyl, quinolinyl or isoquinolinyl; R₃ is hydroxamic acid, hydroxylamino, hydroxyl, amino, alkylamino or alkyloxy group; R₄ is hydrogen, halogen, phenyl or a cycloalkyl moiety; and A can be the same or different and represents an amide moiety, O-, -S-, -NH-, NR₅, -CH₂-, -(CH₂)_m-, -(CH=CH)-, phenylene, cycloalkylene, or any combination thereof wherein R₅ is a substitute or unsubstituted C₁-C₅ alkyl; and n and m are each an integer from 3 to 10.

In further particular embodiment a compounds having a more specific structure within the scope of compounds 2927 or 3028 are is compound 29.²

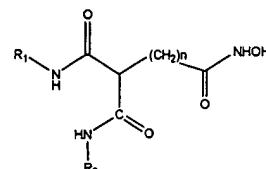
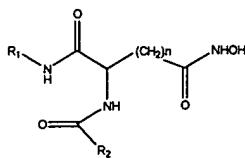
A compound In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 31-29, or a pharmaceutically acceptable salt or hydrate thereof:



(3129)

wherein A is an amide moiety, R₁ and R₂ are each selected from substituted or unsubstituted aryl (e.g., phenyl), arylalkyl (e.g., benzyl), naphthyl, pyridineamino, 9-purine-6-amino, thiazoleamino, aryloxy, arylalkyloxy, pyridyl, quinolinyl or isoquinolinyl; and n is an integer from 3 to 10.

For example, the compound of formula 3029 can have the structure 3130 or 3231:

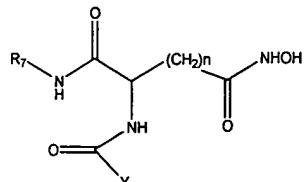


(3130)

(3231)

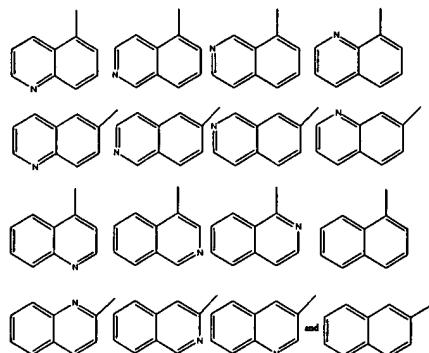
wherein R₁, R₂ and n have the meanings of Formula formula 30-29.

A compoundIn one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 3332 or a pharmaceutically acceptable salt or hydrate thereof:

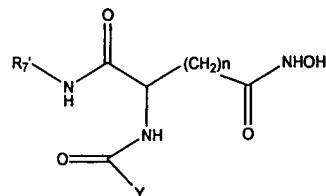


(3332)

wherein R₇ is selected from substituted or unsubstituted aryl (e.g., phenyl), arylalkyl (e.g., benzyl), naphthyl, pyridineamino, 9-purine-6-amino, thiazoleamino, aryloxy, arylalkyloxy, pyridyl, quinolinyl or isoquinolinyl; n is an integer from 3 to 10 and Y is selected from:

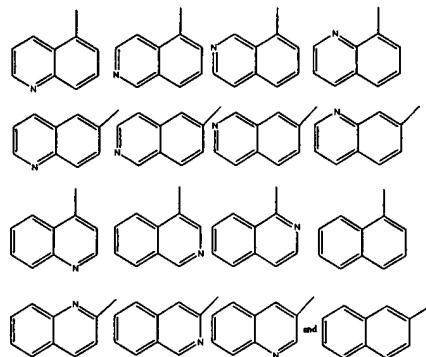


A compoundIn one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 3433 or a pharmaceutically acceptable salt or hydrate thereof:

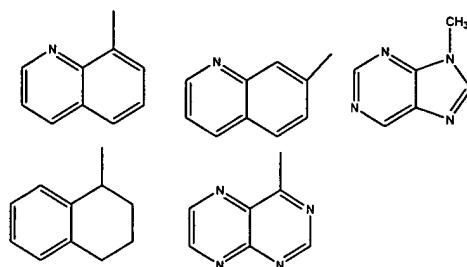


(3433)

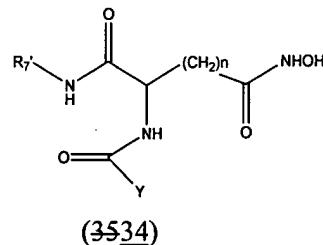
wherein n is an integer from 3 to 10, Y is selected from



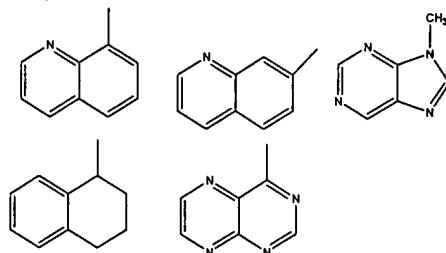
and R^{7'} is selected from



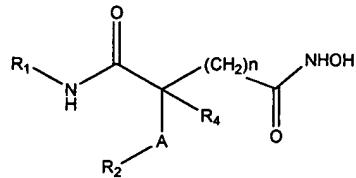
A compound In one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 3534 or a pharmaceutically acceptable salt or hydrate thereof:



aryl (e.g., phenyl), arylalkyl (e.g., benzyl), naphthyl, pyridineamino, 9-purine-6-amino, thiazoleamino, aryloxy, arylalkyloxy, pyridyl, quinolinyl or isoquinolinyl; n is an integer from 3 to 10 and R^{7'} is selected from



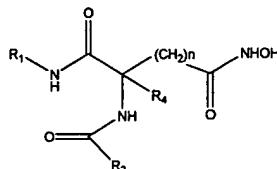
A compoundIn one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 3635 or a pharmaceutically acceptable salt or hydrate thereof:



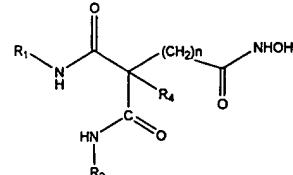
(3635)

wherein A is an amide moiety, R₁ and R₂ are each selected from substituted or unsubstituted aryl (e.g., phenyl), arylalkyl (e.g., benzyl), naphthyl, pyridineamino, 9-purine-6-amino, thiazoleamino, aryloxy, arylalkyloxy, pyridyl, quinolinyl or isoquinolinyl; R₄ is hydrogen, a halogen, a phenyl or a cycloalkyl moiety and n is an integer from 3 to 10.

For example, the compound of formula 3635 can have the structure of formulas 36 or 37 or 38:



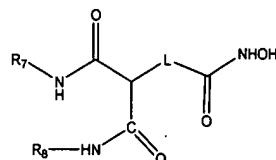
(37 36)



(38 37)

wherein R₁, R₂, R₄ and n have the meanings of Formula formula 36.35.

A compoundIn one embodiment, the HDAC inhibitor useful in the methods of the present invention is represented by the structure of formula 3938 or a pharmaceutically acceptable salt or hydrate thereof:

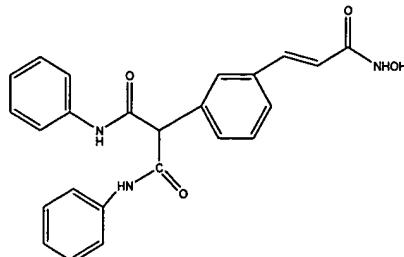


(3938)

wherein L is a linker selected from the group consisting of an amide moiety, O-, -S-, -NH-, NR₅, -CH₂-, -(CH₂)_m-, -(CH=CH)-, phenylene, cycloalkylene, or any combination thereof wherein R₈ is a substitute or unsubstituted C₁-C₅ alkyl; and wherein each of R₇

and R₈ are independently a substituted or unsubstituted aryl (e.g., phenyl), arylalkyl (e.g., benzyl), naphthyl, pyridineamino, 9-purine-6-amino, thiazoleamino, aryloxy, arylalkyloxy, pyridyl, quinolinyl or isoquinolinyl; n is an integer from 3 to 10 and m is an integer from 0-10.

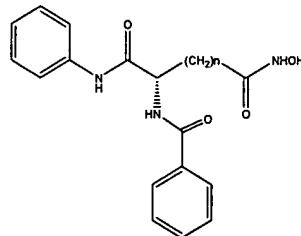
For example, a compound of Formula 3938 can be represented by the structure of formula (39):



(40_39)

Other HDAC inhibitors suitable for use in the methods of the present invention include those shown in the following more specific formulas:

A compound represented by the structure:

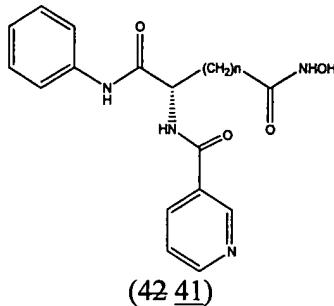


(41_40)

wherein n is an integer from 3 to 10, or an enantiomer thereof. In one particular embodiment of formula 40, n=5.

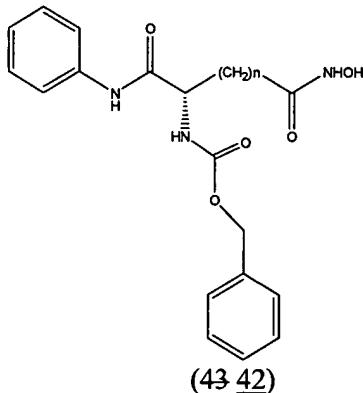
~~Other HDAC inhibitors suitable for use in the invention include those shown in the following more specific formulas:~~

A compound represented by the structure:



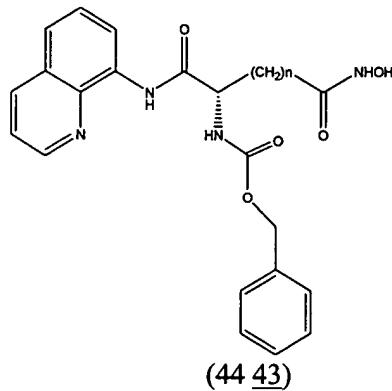
wherein n is an integer from 3 to 10 or an enantiomer thereof. In one particular embodiment of formula 42 41, n=5.

A compound represented by the structure:



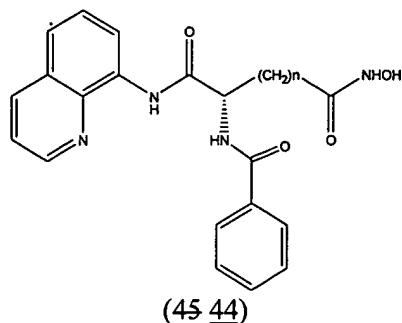
wherein n is an integer from 3 to 10 or an enantiomer thereof. In one particular embodiment of formula 43 42, n=5.

A compound represented by the structure:



wherein n is an integer from 3 to 10, or an enantiomer thereof. In one particular embodiment of formula 44 43, n=5.

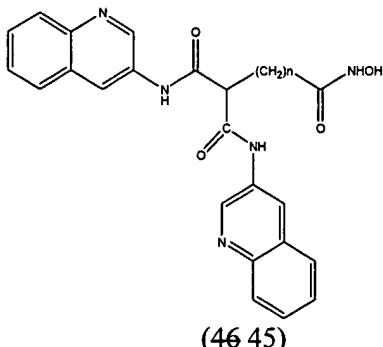
A compound represented by the structure:



(45 44)

wherein n is an integer from 3 to 10 or an enantiomer thereof. In one particular embodiment of formula 45 44, n=5.

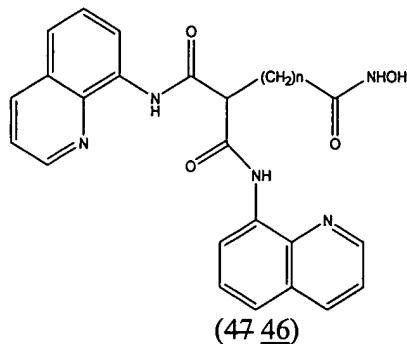
A compound represented by the structure:



(46 45)

wherein n is an integer from 3 to 10 or an enantiomer thereof. In one particular embodiment of formula 46 45, n=5.

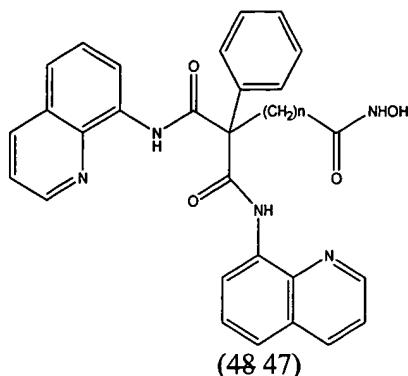
A compound represented by the structure:



(47 46)

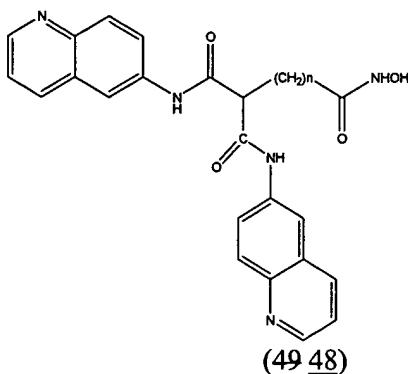
wherein n is an integer from 3 to 10 or an enantiomer thereof. In one particular embodiment of formula 47 46, n=5.

A compound represented by the structure:



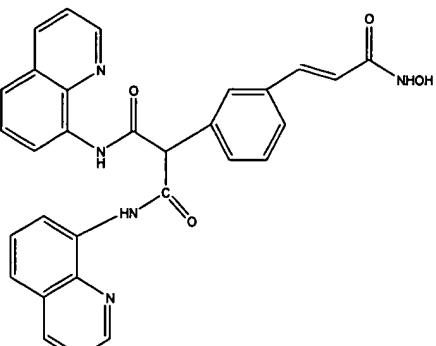
wherein n is an integer from 3 to 10 or an enantiomer thereof. In one particular embodiment of formula 48 47, n=5.

A compound represented by the structure:



wherein n is an integer from 3 to 10 or an enantiomer thereof. In one particular embodiment of formula 49 48, n=5.

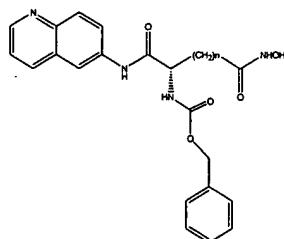
A compound represented by the structure:



(50 49)

wherein n is an integer from 3 to 10 or an enantiomer thereof. In one particular embodiment of formula 50 49, n=5.

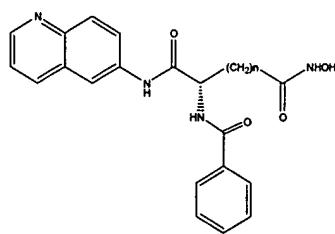
A compound represented by the structure:



(§1 50)

wherein n is an integer from 3 to 10 or an enantiomer thereof. In one particular embodiment of formula §1 50, n=5.

A compound represented by the structure:



(§2 51)

wherein n is an integer from 3 to 10 or an enantiomer thereof. In one particular embodiment of formula §2 51, n=5. --

Please replace the following section beginning at page 45, line 12, ending at page 45, line 20, with the following rewritten section:

-- The invention also encompasses pharmaceutical compositions comprising hydrates of the HDAC inhibitors and/or the anti-cancer agents. The term "hydrate" includes but is not limited to hemihydrate, monohydrate, dihydrate, trihydrate and the like.

~~This~~In addition, this invention also encompasses pharmaceutical compositions comprising any solid or liquid physical form of SAHA or any of the other HDAC inhibitors. For example, The HDAC inhibitors can be in a crystalline form, in amorphous form, and have any particle size. The HDAC inhibitor particles may be micronized, or

may be agglomerated, particulate granules, powders, oils, oily suspensions or any other form of solid or liquid physical form. --

Please replace the paragraph beginning at page 52, line 16, ending on page 52, line 22, with the following rewritten paragraph:

-- II. Syndromes combining progressive dementia with other prominent neurologic abnormalities such as A) syndromes appearing mainly in adults (e.g., Huntington's disease, Multiple system atrophy combining dementia with ataxia and/or manifestations and/or manifestations of Parkinson's disease, Progressive supranuclear palsy (Steel-Richardson-Olszewski), diffuse Lewy body disease, and corticodentatonigral degeneration); and B) syndromes appearing mainly in children or young adults (e.g., Hallervorden-Spatz disease and progressive familial myoclonic epilepsy). --

Please replace the paragraph beginning at page 60, line 5, ending on page 60, line 14, with the following rewritten paragraph:

-- Figures 1 to 8 are HPLC slides showing the amount of α -AcH4 in patients in Cohorts I and II, measured at up to 10 hours after receiving the oral dose, compared with the α -AcH4 levels when SAHA was administered intravenously. Fig 9 shows the mean plasma concentration of SAHA (ng/ml) at the indicated time points following administration. Fig 9A: Oral dose (200 mg and 400 mg) under fasting on Day 8. Fig 9B: Oral dose (200 mg and 400 mg) with food on Day 9. Fig 9C: IV dose on day 1. Fig 10 shows the apparent half-life of a SAHA 200 mg and 400 mg oral dose, on Days 8, 9 and 22. Fig 11 shows the AUC (ng/ml/hr) of a SAHA 200 mg and 400 mg oral dose, on Days 8, 9 and 22. Figure 12 shows the bioavailability of SAHA after a 200 mg and 400 mg oral dose, on Days 8, 9 and 22. --

Please replace the title of Example 3 at page 60, line 17, with the following rewritten title:

-- Oral dosing of suberoylanilide hydroxyamichydroxamic acid (SAHA) – Dose Escalation. --